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P-Chloro-Benzoyl Acetic Ester and some of its Derivatives

Chemical Engineering

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P-CHLORO-BENZOYL ACETIC ESTER
AND
SOME OF ITS DERIVATIVES

BY

EVERETT ROBERT BRUNSKILL

THESIS

FOR THE

DEGREE OF BACHELOR OF SCIENCE

IN

CHEMICAL ENGINEERING

COLLEGE OF LIBERAL ARTS AND SCIENCES

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THIS IS TO CERTIFY THAT THE THESIS PREPARED UNDER MY SUPERVISION BY

EVERETT ROBERT BRUNSKILL

ENTITLED P-CHLORO-BENZOYL ACETIC ESTER AND SOME OF ITS DERIVATIVES

IS APPROVED BY ME AS FULFILLING THIS PART OF THE REQUIREMENTS FOR THE

DEGREE OF Bachelor of Science in Chemical Engineering

Lambert Thorp.
Instructor in Charge

APPROVED: W. A. Noyes

HEAD OF DEPARTMENT OF Chemistry

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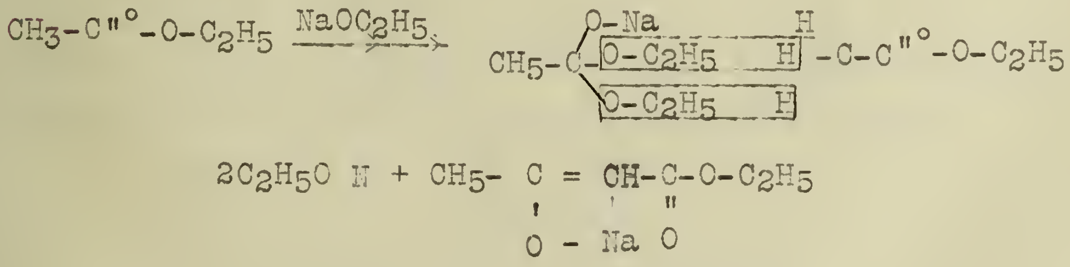
Introduction.

Acetoacetic ester was discovered in 1863 by Geuther who prepared the sodium salt while trying to replace the second hydrogen atom of ethyl acetate with sodium. Because of its method of formation, the mechanism of the reaction has been minutely studied.

The most suitable explanation of the condensation has been offered by Claisen, who found that acetoacetic ester cannot be prepared by the action of sodium on ethyl acetate which has been carefully purified from alcohol. He proved that the sodium first reacted with a trace of alcohol that was present in the ethyl acetate, to form sodium ethylate. The sodium ethylate was then assumed to form an addition product with the ethyl acetate, which then condensed with another mol of ethyl acetate to form the sodium salt of acetoacetic ester.

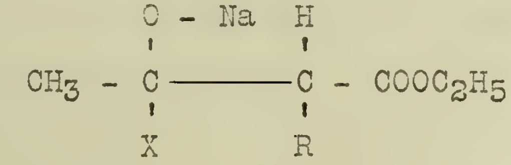


The free ester is obtained by treating the sodium salt with dilute acids.

It can be hydrolysed in two ways, respectively known as the ketone decomposition and the acid decomposition, on account of the nature of the products formed.

It may be mentioned that the reaction by which acetoacetic ester is prepared is one that can be used in the preparation of aldehyde-acids, ketone dicarbonic acid esters, poly ketones, ketone aldehydes, and many other compounds of like nature.

The most remarkable and valuable characteristic of acetoacetic ester is that a portion of its hydrogen may be substituted by metals. If sodium is allowed to act on it, the sodium salt is formed with the elimination of hydrogen. The same salt is also formed by shaking the ester with a solution of sodium hydroxide or sodium ethoxide. The reason for this phenomena is to be sought in the acidifying influence of the neighboring carbonyl group.. The synthetical importance of acetoacetic ester depends on the fact that the most various organic halogen substitution products react with sodium acetoacetic ester, the halogen uniting with the sodium, with the condensation of the two remaining residues. If RX is an organic halide, in which X represents a halogen atom, the product formed with the sodium acetoacetic ester is first:



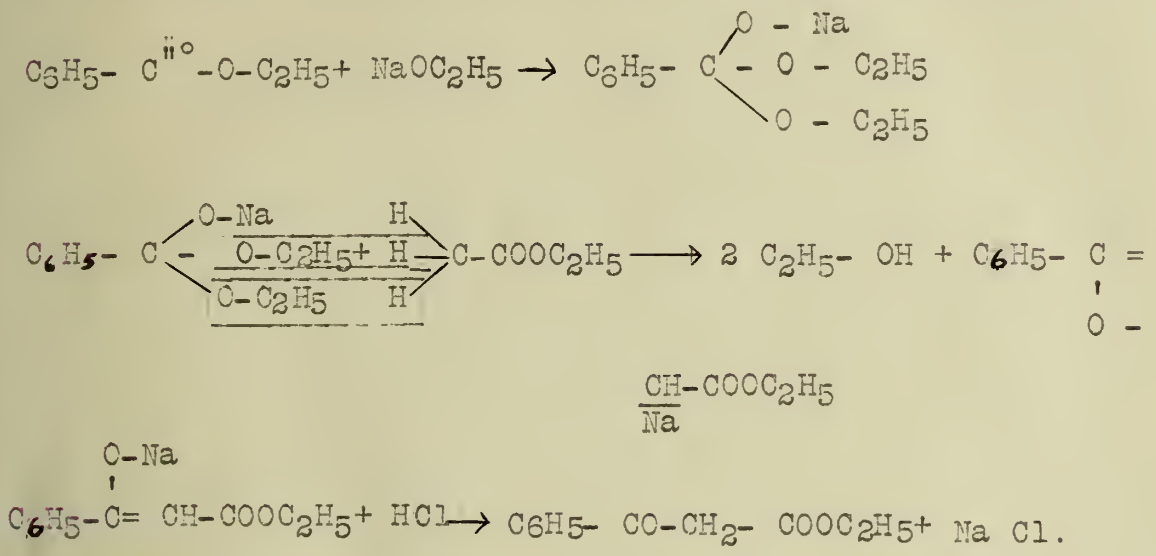
$$\begin{array}{ccccccc} & & O - Na & & H & & \\ & & | & & | & & \\ CH_3 & - & C & \text{———} & C & - & COOC_2H_5 \\ & & | & & | & & \\ & & X & & R & & \end{array}$$

The splitting out of NaX from this yields the compound, $CH_3- CO - CHR - COOC_2H_5$, the hydrogen atom of its - CHR- group being capable of analogous replacement.

Acetoaectic ester may not only be employed for the synthesis of carbon compounds, but it also reacts with nitrogen

compounds, e. g., aldehyde ammonias, phenylhydrazine, aniline, etc.

Benzoylacetic ester may be prepared by the same reaction as that used for acetoacetic ester, as pointed out above.



$$C_3H_5-\overset{O}{\overset{\|}{C}}-O-C_2H_5+NaOC_2H_5 \rightarrow C_6H_5-C\begin{array}{l}O-Na\\ O-C_2H_5\\ O-C_2H_5\end{array}$$

$$C_6H_5-C\begin{array}{l}O-Na\\ O-C_2H_5+\\ O-C_2H_5\end{array}\begin{array}{r}H\\ H\\ H\end{array}C-COOC_2H_5 \longrightarrow 2\ C_2H_5-OH+C_6H_5-\underset{O-}{\underset{|}{C}}=\underset{Na}{CH}-COOC_2H_5$$

$$C_6H_5-\overset{O-Na}{\overset{|}{C}}=CH-COOC_2H_5+HCl \longrightarrow C_6H_5-CO-CH_2-COOC_2H_5+Na\,Cl.$$

The best method for its preparation, however, is the condensation of benzoyl chloride and the sodium salt of acetoacetic ester, with the hydrolysis of the resulting salt by means of ammonia and ammonium chloride.

Benzoyl acetic ester is a very useful compound for organic systhesis, for by the introduction of the proper alkyl groups and subsequent saponification a great number of mono - or polyketones can be prepared.

Origin and Nature of Work.

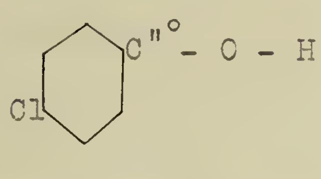
The work presented here is a continuation of that begun by Lambert Thorp upon the halogenated benzoylacetic esters, and had for its object a study of the effect of negative substituents in the aromatic nucleus upon the ease of alkylation and upon the course of the saponification of the substituted benzoylacetic esters. In regard to ease of alkylation chloro benzoyacetic ester stands between benzoylacetic ester and its nitro derivatives, a condition of affairs which might be expected, *a priori*, from other well-known instances of the effect of a substitution of a nitro group for a chlorine atom, such as the relative instability of chloroacetic and nitro acetic acids with respect to the loss of carbon dioxide, the difference in the orientating influence of the halogen atom and the nitro group upon the entrance of a second substituent into the benzene ring, the more pronounced effect of the nitro group upon the reactivity of a halogen atom in the aromatic nucleus.

In this work p-chlorobenzoylacetoacetic ester was prepared by the condensation of the sodium salt of acetoacetic ester and p-chlorobenzoyl chloride. The sodium salt of p-chlorobenzoylacetoacetic ester was then hydrolyzed by means of ammonia and ammonium chloride to sodium acetate and p-chlorobenzoylacetic ester. The p-chlorobenzoyl chloride was prepared by the oxidation of p-chlorotoluene to p-chlorobenzoic acid and subsequent treatment of this with phosphorous penta chloride to form p-chlorobenzoyl chloride. An attempt was made to saponify the p-chlorobenzoylacetic ester with potassium hydroxide, but it was found that a potassium salt of p-chloro benzoyl acetic ester

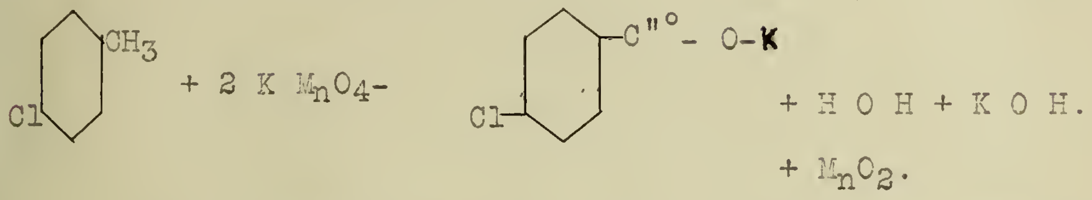
was formed before the alcohol radicle was split off. However, by a more prolonged treatment with potassium hydroxide solution the ester was saponified and p-chlorobenzoylacetic acid obtained. Its physical properties and solubility reactions were determined. The next step was the alkylation of p-chlorobenzoyl acetic ester with brom-methyl-phenyl ketone. The resulting compound was then saponified to form p-chlorodiphenacyl. In order to determine the place effect of chlorine p-chlorodiphenacyl was also prepared by the alkylation of benzoylacetic ester with p-chlorophenyl-methyl ketone, and the resulting compound saponified. A difference in the relative ease of alkylation and saponification was noted here.

Experimental.

P-Chlorobenzoic Acid.



This acid was prepared by the oxidation of p-chlorotoluene with a solution of potassium permanganate, in accordance with the following reaction:

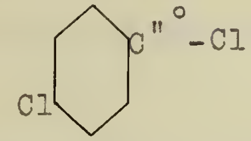


Fifty grams of p-chlorotoluene, 150 grams of potassium permanganate, and five **liters** of water were heated in a tim boiler fitted with a reflux condenser, until the potassium permanganate was all reduced. The slight excess of p-chlorotoluene was then removed by steam distillation, and the manganese dioxide in the residue allowed to settle afterwards. The clear supernatant liquid was then **decanted** thru a Buchner funnel. The residue was washed twice with boiling water, the wash water being **decanted** thru the funnel each time. The residue was then washed onto the funnel, sucked dry and strongly compressed.

The filtrate was cooled and treated with the calculated amount of cold concentrated hydrochloric acid, whereby the p-chlorobenzoic acid was precipitated. This was then filtered by means of suction and washed with water until the wash water no longer gave a test for chlorine. The acid was then dried

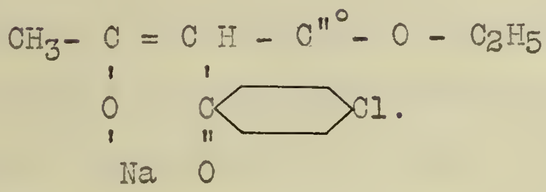
on the water bath. Four hundred and twenty-five grams of p-chlorotoluene were oxidized in this manner. The yield of p-chlorobenzoic acid was 396 grams or 75% of the theoretical. The melting point was 236.8°C, which compares favorably with that given in the literature, which is 263-237°C.

P-Chlorobenzoyl Chloride.



This substance was prepared by the usual method for the preparation of acid chlorides. One hundred grams of p-chlorobenzoic acid was placed in a 700 cc. round bottom flask and then treated with a two gram excess of the calculated amount (133 grs.) of phosphorous pentachloride in three portions. Toward the end of the reaction it was necessary to heat the mixture on a water bath. After the acid had all disappeared the mixture was fractionated. Two fractions were taken, 105 - 180 ° C, and 180 - 226 ° C. The last fraction practically all came over at 225-226° and was tinged faintly yellow, whereas the original mixture was an orange red. The higher boiling fraction was again fractioned into two parts, 80-200°C, and 200-225°C. The last fraction boiled almost constantly at 225° and was colorless. The yield was 99 grams or 88.6% of the theoretical.

Sodium Salt of P-Chlorobenzoyl Acetoacetic Ethyl Ester.



To one-half (100 cc.) of a solution of sodium ethylate, prepared by dissolving 13.12 grams (2 mols) of sodium in 200 cc. of absolute alcohol, 37 grams of acetoacetic ester (1 mol) was added. The solution of sodium acetoacetic ester, so obtained, was cooled to 5°C, and then one-half of a solution of 50 grams (1 mol) of p-chlorobenzoyl chloride dissolved in 90 cc. of dry ether, were added gradually from a burette, the temperature of the reaction mixture being kept under 10°. It is essential that the solution be constantly stirred during the addition. After the lapse of a half hour 50 cc. of sodium ethylate solution were added and, when the temperature of the mixture had again fallen to 5°, one-half of the remaining amount of p-chloro-benzoyl chloride was added as before. In this manner, always employing one-half of the remaining sodium ethylate solution and p-chlorobenzoyl chloride, the operation was completed after six additions. In order that the separation of the sodium salt might be complete, the reaction mixture was allowed to remain in a cold place for 24 hours. The salt was then filtered with the aid of suction and washed several times with dry ether.

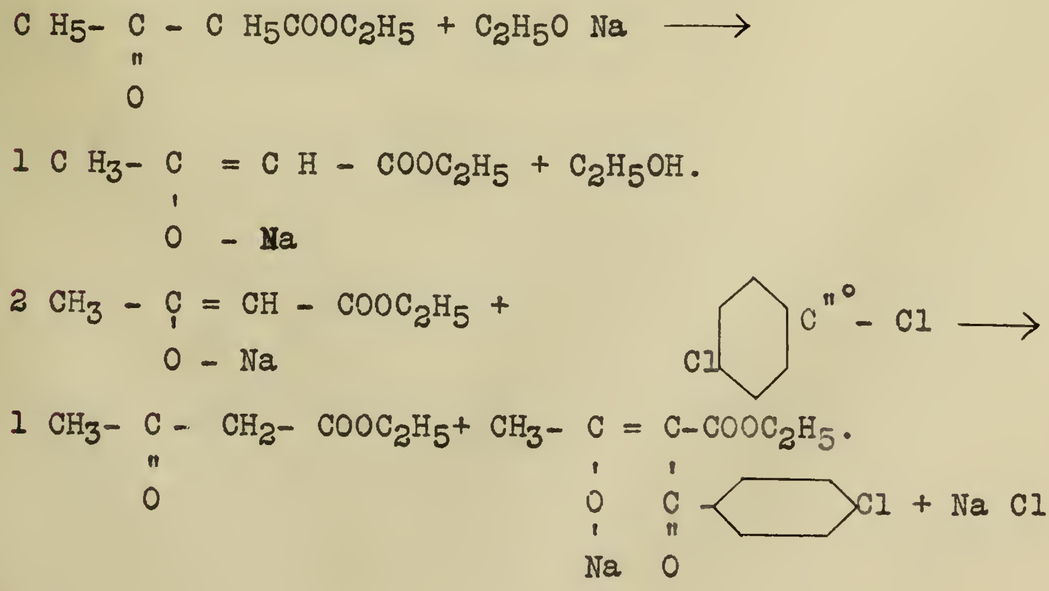
The yield was 90 grams or 90% of the theoretical. This salt is of a yellow color and quite insoluble in water.

According to this method, as is shown by the following reactions, one-half of the sodium acetoacetic ester present is transformed into acetoacetic ester, consequently further additions of sodium ethylate are made to reform the sodium salt, and this in turn is allowed to react with the acid chloride, which is added as soon as the proper temperature is reached. The course of the reaction may be indicated as follows:

2 sodium acetoacetic ester + p-chlorobenzoylchloride,
⟶ Sodium chloride + 1 acetoacetic ester + 1 sodium salt
of p-chlorobenzoyl acetoacetic ester.

The structural reactions are as follows:

$$2\ C_2H_5OH + 2\ Na \longrightarrow 2\ C_2H_5O\,Na + H_2$$

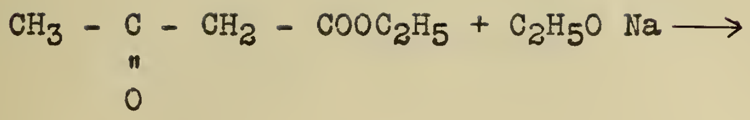


$$C\,H_5-\underset{\overset{\|}{O}}{C}-C\,H_5COOC_2H_5 + C_2H_5O\,Na \longrightarrow$$

$$1\ C\,H_3-\underset{\overset{|}{O}\,-\,Na}{C}=C\,H-COOC_2H_5 + C_2H_5OH.$$

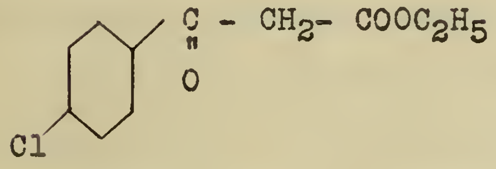
$$2\ CH_3-\underset{\overset{|}{O}\,-\,Na}{C}=CH-COOC_2H_5 +$$

$$1\ CH_3-\underset{\overset{\|}{O}}{C}-CH_2-COOC_2H_5+CH_3-\underset{\underset{Na}{\overset{|}{O}}}{C}=C-COOC_2H_5. \quad + Na\,Cl.$$

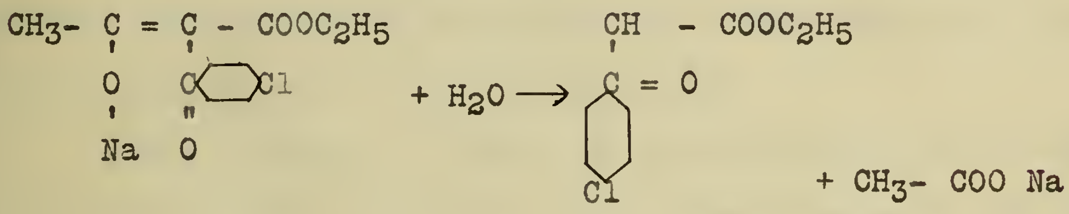


$CH_3 - \underset{\underset{O}{\|}}{C} - CH_2 - COOC_2H_5 + C_2H_5O\,Na \longrightarrow$ give the second and third reactions again.

P-Chlorobenzoylacetic Ester.



This ester was prepared in accordance with the following scheme for the hydrolysis of the sodium salt of p-chlorobenzoylacetoacetic ester.



One hundred and twenty grams of the sodium salt were suspended in 600 cc. of water, 30 grams of ammonium chloride and 60 cc. of concentrated aqueous ammonia were added, and the mixture maintained at a temperature of 40-45° for three hours, with continual shaking. At the end of this time all the salt had disappeared and a heavy yellowish oil had taken its place in the bottom of the flask. The contents of the flask were cooled and the oil extracted with ether. The etheral solution was dried over calcium chloride, and the ether then distilled off. In this manner the ester was obtained as a yellow viscous oil, which upon being cooled in a freezing mixture solidified to a mass of crystals. The crystals were pressed out on a porous plate and then recrystalized until a constant melting point was obtained.

The yield was 69.5% of the theoretical.

P-chlorobenzoylacetic ester crystallizes from dilute alcohol in the form of colorless flat prisms, and has a melting point of 38°. It is insoluble in water, readily soluble in alcohol, ether, benzene, or ligroin.

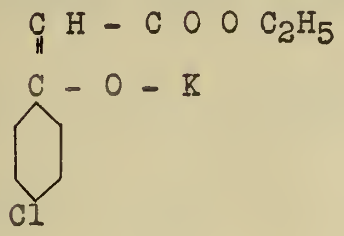
0.4387 grs. sub. gave 0.2880 grams Ag Cl.

Calc. for $C_{11}\ H_{11}\ O\ Cl$: Cl, 15.67% : found, 15.79%.

The chlorine determinations in this work were made by means of burning the compounds with sodium peroxide and potassium nitrate in a Parr Sulphur bomb.

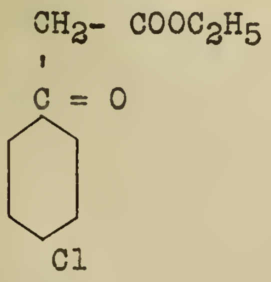
A small amount of sodium peroxide was placed in the bottom of the bomb, and then the weighed substance and about a gram and a half of potassium nitrate were added. The bomb was then filled about three quarters full with sodium peroxide, closed, and heated strongly for five minutes. It was then cooled and the excess sodium peroxide decomposed with water. The water solution was then acidified with concentrated nitric acid and boiled to get rid of any hydrocyanic acid that may have been formed. The chlorine was then precipitated and weighed in the usual manner.

Potassium Salt of P-chlorobenzoyl Acetic Ester.

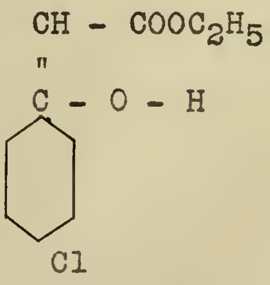


Upon treating five grams of p-chlorobenzoylacetic ester with two equivalent weights of potassium hydroxide in a 10% solution at room temperature, a white voluminous precipitate came down. This was filtered off and recrystallized from absolute alcohol. When a small amount of the precipitate was burned upon a platinum foil a residue was obtained.

Since in the formula assigned to the p-chlorobenzoylacetic ester, there is a double bonded oxygen attached to a carbon atom, it is consistent with the theories of tautomerism to assume that p-chlorobenzoylacetic ester exists in two forms. The two structures that are possible are:

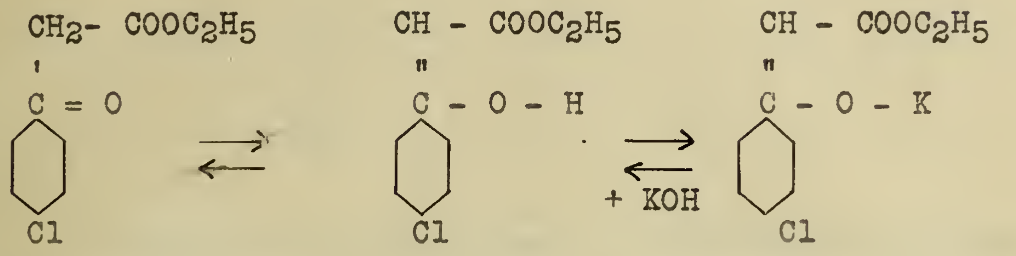


Ketone Form.



Enolic Form.

Assuming an enolic structure the formation of a potassium salt can be easily explained.



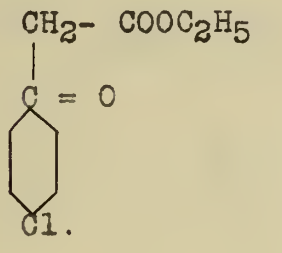
A potassium determination confirms the above hypothesis.

0.2132 grs. sub. gave 0.0682 grams K_2SO_4.

Calc. for $C_{11}H_{10}O_3ClK$: K, 14.37%: found 14.78%

The salt is slightly soluble in water, and easily soluble in alcohol. It melts with decomposition at 265°.

P-chlorobenzoyl acetic Acid.



Three and one-half grams of p-chlorobenzoylacetic ester were allowed to react with 2.4 grams (3 mols) of potassium hydroxide for a period of three days. At the end of this time the solution was filtered, and then extracted with ether in order to remove traces of unchanged ester and p-chloroacetophenone. From the cold solution the p-chlorobenzoylacetic acid was precipitated by means of dilute sulphuric acid. It was filtered and sucked dry. The acid was then recrystallized from a mixture of ether and ligroin.

P-chlorobenzoylacetic acid is very slightly soluble in water; slightly soluble in benzene or ligroin; readily soluble in alcohol or ether.

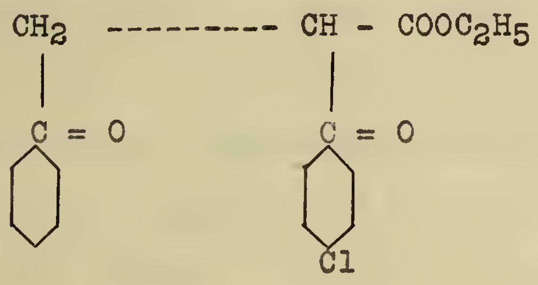
When heated gradually the substance decomposes into p-chloroacetophenone; but when quickly brought to a temperature in the vicinity of its melting point it melts at 232°.

0.0784 grs. sub. gave 0.0568 grams Ag Cl.

Calc. for $C_9H_7O_3Cl$; Cl, 17.88%: found, 17.89%.

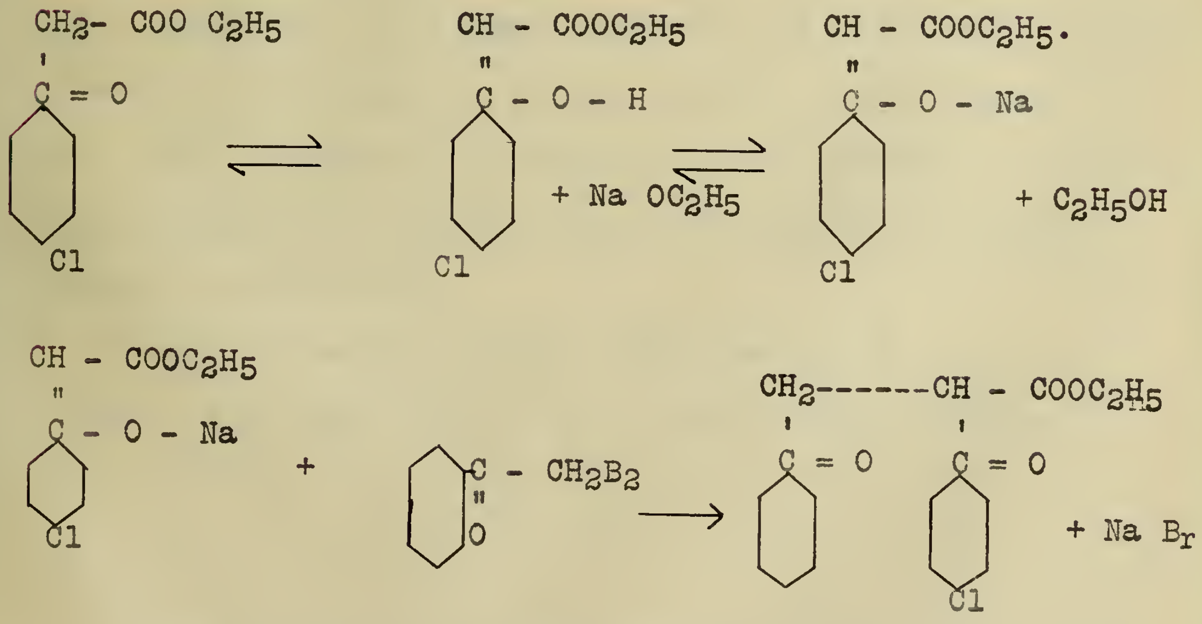
Alkylation of P-Chlorobenzoylacetic Ester.

Phenacyl p-chlorobenzoylacetic Ethyl Ester.



This ester was prepared in accordance with the following scheme:

$2\ C_2H_5\ O\ H\ +\ 2\ Na \qquad 2\ C_2H_5\ O\ Na\ +\ H_2.$



To a solution of sodium ethylate prepared from 2.05 grams of sodium and 35 cc. of absolute alcohol, 20 grams of p-chlorobenzoylacetic ester were added. The solution of the sodium salt of p-chlorobenzoylacetic ester was cooled and

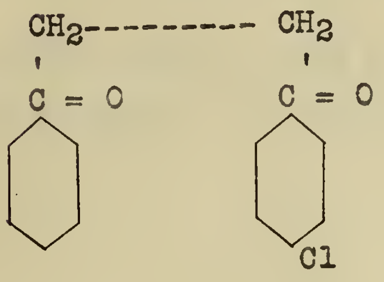
then gradually treated with one equivalent weight (17.6 grs.) of phenacyl bromide. The solution turned red in color with evolution of heat and separation of sodium bromide. The reaction was driven to completion by warming on the water bath for fifteen minutes. Water was then added to dissolve the sodium bromide, and the reddish oil which separated was taken up with ether. The etheral solution was dried over calcium chloride, filtered, and the ether removed by distillation. The residual oil, after being allowed to remain in a cold place for several days, was transformed into a crystallized mass. The crystals were pressed out on a porous plate and then re-crystallized from dilute alcohol. The yield was 50% of the theoretical.

Phenacyl p-chlorobenzoylacetic ethyl ester crystallizes in the form of colorless prisms, and has a melting point of 63°. It is insoluble in water, slightly soluble in ligroin, fairly soluble in alcohol, and readily soluble in ether, benzene or chloroform.

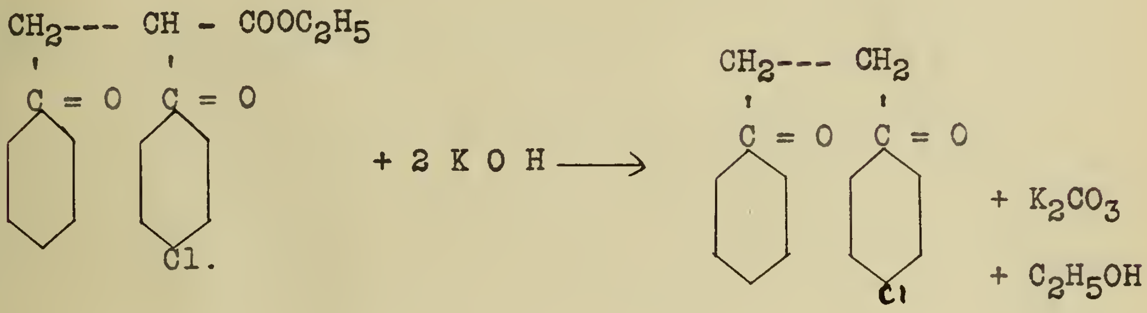
0.2238 grams sub. gave 0.1342 gram Ag Cl.

Calc. for $C_{19}H_{17}O_4Cl$: Cl, 10.33%: found, 10.36%.

4-Chlorodiphenacyl.



This substance was prepared by the saponification of phenacyl p-chlorobenzoylacetic ester.



Thirty-five grams of phenacyl p-chlorobenzoylacetic ester were added to a solution of 13.6 grams of potassium hydroxide (2 mols) in a mixture of 300 cc. of water and 100 cc. of alcohol. The mixture was then boiled under a reflux condenser. After two hours boiling the contents of the flask were cooled, and the product filtered off. Several recrystallizations from alcohol, with the aid of bone-black, gave a pure product melting at 114.5°. The yield was poor.

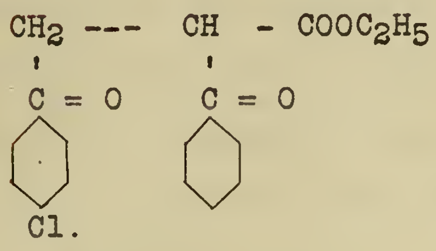
4-chlorodiphenacyl crystallizes in the form of colorless leaflets of pearly lustre. It is insoluble in water, slightly soluble in ligroin, fairly soluble in alcohol and

ether, and readily soluble in benzene or chloroform.

0.3378 grams sub. gave 0.1814 grams Ag Cl.

Calc. for $C_{16}H_{13}O_2Cl$: Cl, 13.02%: found, 13.28%.

P-Chlorophenacyl Benzoylacetic Ethyl Ester.



This ester was prepared in order to determine the relative yields of 1, 4-diketone produced in the saponification of this and the isomeric ester described above.

Thirty-eight grams of p-chlorophenacyl bromide were added gradually to a solution of the sodium salt of benzoylacetic ester, prepared from 3.65 grams of sodium, 80 cc. of absolute alcohol, and 30 grams of benzoylacetic ester.

The p-chlorophenacyl bromide was prepared by dissolving 38.5 grams of p-chloroacetophenone in an equal volume of carbon-disulphide and then adding 20 grams of bromine dissolved in 80 cc. of glacial acetic acid. The mixture was then heated on the water bath to 40°. In a short time a vigorous reaction set in, the temperature rose rapidly and a great volume of hydrobromic acid was evolved. After the reaction was complete the mixture was poured into 500 cc. of cold water, whereby the p-chlorophenacyl bromide was precipitated. It was then filtered off with the aid of suction. The yield was 74% of the theoretical.

The reaction was completed by warming on the water bath for a half hour. The alcohol was then distilled off and enough water added to dissolve the sodium bromide. The oil which separated was extracted with ether and the etheral solution dried over calcium chloride. It was then filtered and the ether distilled off on the water bath. In order to remove the last traces of ether the ester was placed in vacuo over sulphuric acid, a procedure which caused the transformation of the substance into a crystalline mass. The product was pressed out on a porous plate, and then recrystallized from alcohol. The yield was 75% of the theoretical.

P-chlorophenacylbenzoylacetic ethyl ester crystallizes in the form of colorless needles which have a melting point of 92°. It is insoluble in water, fairly soluble in alcohol, ether or ligroin; readily soluble in benzene, or chloroform.

0.2084 grams sub. gave 0.0892 grams Ag Cl.

Calc. for $C_{19}H_{17}O_4Cl$: Cl, 10.33%: found, 10.58%.

Saponification of 9 grams of the ester by means of a solution of 3.2 grams of potassium hydroxide in a mixture of 75 cc. of water and 25 cc. of alcohol yielded 50% of the theoretical amount of a substance identical in melting point, and undistinguishable in other physical properties from the 4-chlorodiphenacyl described above.

SUMMARY.

In this research p-chlorobenzoylacetic ester and certain of its derivatives were prepared.

It was also found that thebyield of p-chlorodiphenacyl when prepared by the alkylation of ebnzoylacetic ester was much better than when prepared by the alkylation of p-chlorobenzoylacetic ester. In thesaponification of the resulting alkyl compounds it was found that the p-chlorophenacyl-benzoylacetic ester was more easily saponified than the phenacyl p-chlorobenzoylacetic ester. As one of these compounds is the isomer of the other the difference in case of formation must be directly due to the existence of the halogen atom in the benzene nucleus.

Acknowledgement: - I take occasion here to thank Dr. Thorp for the invaluable assistance he has rendered to me in the preparation, and in the work leading toward the preparation of this thesis.

E. R. Brunskill.

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